Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 8, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.01.106

ASK NOT What CRP Can Do for You*

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The clinical utility of high-sensitivity C-reactive protein (hsCRP) testing in patients being considered for statin therapy or already taking statins is an area of intense interest. Creative avenues of investigation into the vascular biology of inflammation have taken the concept of atherosclerotic plaque formation from passive lipid deposition to an interactive process of lipids networking with the innate and adaptive immune systems. Amid a rich body of basic, translational, and clinical science, the idea of bringing inflammation to the bedside in preventing and treating atherosclerotic cardiovascular disease (CVD) continues to stir controversy.

In this issue of the *Journal*, Sever et al. (1) evaluate the

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relationship of baseline and on-treatment hsCRP levels with cardiovascular events among hypertensive patients in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm). As has been demonstrated in multiple previous prospective studies, baseline hsCRP levels predicted incident CVD. However, across tertiles of baseline hsCRP levels, no difference was detected in the relative effect of statin therapy. After 6 months of atorvastatin 10 mg/day, median levels of hsCRP dropped by 26% and low-density lipoprotein cholesterol (LDL-C) by 39%. Although achieving LDL-C levels below the median at 6 months was associated with lower CVD risk, a clear risk reduction was not seen for hsCRP levels below the median.

The current report extends the findings of an earlier nested case-control ASCOT study (2) indicating that baseline and on-treatment hsCRP levels may not meaningfully predict benefit of statins. The newest report incorporates increased statistical power with 456 major CVD events included in baseline analyses and 170 cases in on-treatment analyses. Similar to the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, the ASCOT-LLA takes place in the primary prevention setting, although the baseline mean LDL-C was higher (129 mg/dl vs. 104 mg/dl) and hsCRP was lower (2.4 vs. 4.2 mg/l) in the ASCOT-LLA versus the JUPITER (3).

Having just taken part in another historical presidential election in the United States, it seems fitting to reflect on the Inaugural Presidential Address of John F. Kennedy. On January 20, 1961, he proclaimed, "ask not what your country can do for you—ask what you can do for your country." In the same vein, of the ASCOT, might we say, ASK NOT what CRP can do for you—ask what you can do for your CRP? We can imagine that if President Obama was briefed on this ASCOT-LLA report and asked to prioritize national resources for routine serial hsCRP testing in the primary prevention setting, he might react with his "McKayla Maroney is not impressed" face.

Nevertheless, this report from the ASCOT-LLA is observational and has other significant limitations that must be considered. Despite the large overall number of events, a more limited number of cases had on-treatment hsCRP data. As shown in Table 4, on-treatment hsCRP levels below the median were associated with consistent trends toward benefit, with nonsignificant risk reductions of 34% for coronary heart disease (CHD) events and 22% for CVD events in fully adjusted models. As has been suggested previously (4), it remains possible that with greater statistical power, significant reductions in CVD might have been observed. This notion is supported by an analysis using imputed data for missing covariates (Table 5), which contained additional events and demonstrated that achieved hsCRP levels less than the median were associated with a significant 39% reduction in CHD events and a 30% reduction in CVD events bordering on statistical significance ($p = 0.07$). Post hoc analysis of the JUPITER, better powered for on-treatment analyses, suggests that lower hsCRP levels may indicate greater degrees of success with statin treatment (5).

In addition, the ASCOT-LLA population is >80% men, entirely white, and older in age; given known demographic variations in hsCRP levels, the results might not be fully generalizable to women, nonwhite ethnicities, or younger patients. Furthermore, the results of serial hsCRP assessments in this primary prevention trial may also not be generalizable to post-ACS or CHD patients, settings where lower on-treatment hsCRP levels have been associated with reduced risk.

There is inconsistent evidence regarding the utility of hsCRP measurements for targeting statin therapy for primary

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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prevention. In the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), baseline hsCRP levels differentiated which patients with relatively low LDL-C levels benefited from statin therapy (6). In contrast, in the Heart Protection Study of 20,536 at-risk individuals bridging the primary and secondary prevention spheres, statin therapy conferred a 29% relative risk reduction even if baseline hsCRP was <1.25 mg/l (7). In the analysis by Sever et al. (1) of the ASCOT-LLA, participants showed similar proportional statin effects across baseline hsCRP levels. The 2010 American College of Cardiology Foundation/American Heart Association guidelines on Assessment of Risk in Asymptomatic Adults give a Class IIa indication to measure hsCRP in persons meeting JUPITER entry criteria (8). Ultimately, however, the absolute statin benefit depends on absolute risk, to which hsCRP adds modest incremental information to clinical metrics already in routine use (9).

Regarding hsCRP testing to guide ongoing statin therapy in the primary prevention setting, in the absence of a trial randomizing patients to on-treatment hsCRP monitoring or not, studies like the current ASCOT-LLA are helpful to inform clinical practice. In a cost-constrained healthcare system, it is crucial to appraise these existing data to assess whether the information gained from sending an hsCRP level justifies the added cost of ~$30 (10).

At the population-level, statin therapy lowered hsCRP levels by 26% in the ASCOT-LLA and 37% in the JUPITER (2). Closer to the bedside, at the patient-level, some studies suggest a heterogeneous response of hsCRP levels to statins with 30% to 40% of patients seeing no change or an increase in hsCRP on treatment (11). Moreover, a lingering fundamental issue is the potential lack of causality of CRP in CVD suggested by Mendelian randomization (in contrast to LDL-C) (12). Moreover, a previous meta-regression analysis found that the degree of risk reduction conferred by statins is completely compatible with the degree of LDL-C lowering rather than additional pleiotropic effects (13). Thus, available data do not provide conclusive evidence to support widespread use of serial hsCRP testing (14).

The most appropriate question may be to ask what you can do for your hsCRP because lifestyle improvements are the cornerstone of prevention, and they consistently lower inflammatory biomarkers. Moreover, even if CRP is not a causal risk factor, it reflects underlying inflammatory processes that might be causal and modifiable with pharmacotherapy. On this frontier, exciting work is under way. Two cardiovascular inflammation reduction trials will test the impact of canakinumab (monoclonal antibody to interleukin-1β) and low-dose methotrexate on clinical outcomes. We hope that these innovative trials yield new therapeutic options for our patients.

In the meantime, we are indebted to the pioneering scientists who have moved the inflammatory hypothesis forward, and we find the current ASCOT-LLA report valuable in placing serial laboratory quantification of systemic inflammation in a clinical context. But like the recent presidential debates, this report will add to the intensely partisan conversations regarding the utility of hsCRP testing in guiding statin therapy without yielding any definitive consensus for practice. Clinicians will ultimately cast their votes in the form of lab orders (or the lack thereof). In the meantime, we are optimistic that future patient-oriented discoveries will help bring the concepts of vascular inflammation closer to the bedside and make for a more informed electorate.

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Key Words: cohort ■ C-reactive protein ■ study.